vivo expansion of a murine HSC comprising transducing the murine HSC with a nucleic acid encoding any ABC transporter and a human HSC comprising transducing the human HSC with any ABC transporter for a period up to 3 days does not reasonably provide enablement for a method of performing ex vivo expansion of any HSC for instance a human HSC comprising transducing the human HSC with any ABC promoter using any vector and culturing the gene modified human HSC with any ABC promoter using any vector and culturing the gene modified human HSC so as to expand the modified human HSC for at least 9 days. Applicants respectfully disagree with the Examiner's suggestion that the recited claims are not allowable under 35 U.S.C. § 112, first paragraph.

Hematopoietic stem cells (HSC) from mammals including primates and particularly humans, can be successfully transduced using methods available in the art as of the priority date for this application of May 28, 1998. Non-human primate HSCs, a very good model of human stem cells can be transduced with retroviral vectors at frequencies up to five percent. For example, Dunbar et al. 1996 Proc. Natl. Acad. Sci.,USA, Vol 93 pp 11871-11876; and Tisdale et al. 1998 Blood 92:1131-1141 disclose successful transduction methods permitting gene transfer in HCSs with favorable transfer efficiencies. Further, it has also been shown

that human stem cells can be transduced with vectors at a low frequency and recent studies have shown that transduction rates of up to fifteen percent can be achieved in human patients.

In addition, the success of the claimed invention does not depend on a high transduction frequency. Even if a low but detectable proportion of stem cells are transduced, it is the ABC transporter mediated expansion of these cells which allows for amplification and expansion, thereby providing a powerful tool for overcoming low gene transfer rates into stem cells. Accordingly, it is clear that a skilled artisan could insert and express an ABC transporter gene in human hematopoietic cells and expand the HSC's ex vivo according to the teachings provided in the application in view of the state of the art as of the priority date.

In light of the foregoing remarks Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

II. Rejection of Claims under 35 U.S.C. §112, second paragraph

Claim 4 has been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants

regard as the invention. The Examiner has suggested that there is insufficient antecedent basis for the limitation "cytokine" in claim 4. In response to the Examiner's suggestion, Applicants have amended claim 4 to recite dependency upon claim 3, and thereby provide requisite antecedent basis.

Applicants respectfully request withdrawal of this rejection.

III. Rejection of Claims under 35 U.S.C. § 102

The Examiner has rejected claims 1-12, and 14 under 35 U.S.C. § 102(b) as being anticipated by McDonagh, K(W/O 99/14613). The Examiner has rejected claims 1-12, and 14 under 35 U.S.C. § 102(e) as being anticipated by McDonagh, K.(U.S. Patent No. 5,837,536).

The Examiner suggests that the base claim is directed to a method for performing ex vivo expansion of HSC with a gene encoding an ABC transporter and the subsequent expansion of the HSC comprising the ABC transporter. McDonagh et al. is suggested to teach ex vivo expansion of HSC comprising a MDR1 gene that is expanded 10 fold in 72 hours. McDonagh et al. is further suggested to teach expansion in the presence of a cytokine such as interleukin-3 and interleukin 6. McDonagh et al. is yet

further suggested to teach a DNA sequence for a human MDR1 gene which encodes p-glycoprotein wherein at least one base in a splice region of the DNA encoding the p-glycoprotein is changed such that no truncation of the p-glycoprotein occurs upon expression, McDonagh et al. is still further suggested to teach retroviral vectors such as Harvey Murine Sarcoma vector, adenoviral vectors and AAVs for use in the method of transducing a HSC. McDonagh et al. is still further suggested to refer to prior art teachings wherein retroviral vectors are used to transfer and express MDR1 gene in murine hematopoietic cells. McDonagh et al. is further suggested to anticipate that primate cells may be genetically engineered and in particular for applications for the use of repopulating primate HSCs which are genetically engineered with DNA encoding MDR. Applicants traverse this rejection.

To anticipate a claim the reference must teach each and every element of the claim. MPEP 2131. The identical invention must be shown in as complete detail as is contained in the . . . claim. *Richardson v. Suzuki Motor Co.*, 868 F2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The present application teaches a method of performing ex vivo expansion of a gene modified hematopoietic stem cell

comprising transducing a hematopoietic stem cell with a nucleic acid encoding an AEC transporter selected from a group consisting of MDR1 and BCRP; and then culturing the gene-modified hematopoietic stem cell ex vivo.

The Examiner's suggestion that McDonagh et al. teach ex vivo expansion of HSCs is not an accurate representation of the teachings of McDonagh et al. The expansion of cells in McDonagh et al. (column 15, line 31) simply reflects the effects of hematopoietic cytokines on committed progenitor cells and does not require the MDF1 vector or reflect an expansion of true repopulating cells. Expansion of gene modified HSCs would not have occurred in this example because the retroviral promoter used to express the MDR1 gene in the G1MD11 AA1.2 vector (the promoter derived from the Moloney Murine Leukemia Virus) does not promote expression in primitive stem cells. As a result, **expansion of HSC's would not occur** because there would be no expression of the ABC transporter MDR1 in the primitive stem cells.

While the McDonagh et al. patent does mention the use of a Harvey-based MDR1 vector at column 3, line 66, as well as the use of other promoters, e.g. column 4, lines 44-55, there is no

teaching that HSCs modified to express an ABC transporter could be preferentially expanded ex vivo. Thus, McDonagh et al. does not provide sufficient detail to enable one of skill to make and use the present invention. Thus, the teachings of McDonagh et al. would not allow one skilled in the art to arrive at the claimed invention and thus could not constitute anticipation.

Withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claim 2 has been canceled.

Claim 4 has been amended as follows:

4. (Amended) The method of claim ~~1~~ 3 wherein the cytokine is selected from the group of cytokines consisting of interleukin-3, interleukin-6, G-CSF, GM-CSF, FLT-3 ligand, and stem cell factor.